

(3) Is safe for intravenous injection.

(c) *Microbial contamination.* All processing steps shall be conducted in a manner to minimize the risk of contamination from microorganisms, pyrogens, or other impurities. Preservatives to inhibit growth of microorganisms shall not be used during processing.

(d) *Storage of bulk fraction.* Bulk concentrate to be held more than 1 week prior to further processing shall be stored in clearly identified closed vessels at a temperature of  $-5^{\circ}\text{C}$  or colder. Any other bulk form of the product (exclusive of the sterile bulk solution) to be held more than 1 week prior to further processing, shall be stored in clearly identified closed vessels at a temperature of  $5^{\circ}\text{C}$  or colder. Any bulk fraction to be held one week or less prior to further processing shall be stored in clearly identified closed vessels at a temperature of  $5^{\circ}\text{C}$  or colder.

(e) *Heat treatment.* Heating of the final containers of Plasma Protein Fraction (Human) shall begin within 24 hours after completion of filling. Heat treatment shall be conducted so that the solution is heated continuously for not less than 10 or more than 11 hours at an attained temperature of  $60\pm 0.5^{\circ}\text{C}$ .

(f) *Stabilizer.* Either  $0.08\pm 0.016$  millimole sodium caprylate, or  $0.08\pm 0.016$  millimole sodium acetyltryptophanate and  $0.08\pm 0.016$  millimole sodium caprylate per gram of protein shall be present as a stabilizer(s). Calculations of the stabilizer concentration may employ the labeled value 5 percent for the protein concentration of the product.

(g) *Incubation.* All final containers of Plasma Protein Fraction (Human) shall be incubated at  $20$  to  $35^{\circ}\text{C}$  for at least 14 days following the heat treatment prescribed in paragraph (e) of this section. At the end of this incubation period, each final container shall be examined and all containers showing any indication of turbidity or microbial contamination shall not be issued. The contents of turbid final containers shall be examined microscopically and tested for sterility. If growth occurs, the types of organisms shall be identified as to genus and the material from

such containers shall not be used for further manufacturing.

[42 FR 27583, May 31, 1977, as amended at 64 FR 26286, May 14, 1999]

#### § 640.92 Tests on final product.

Tests shall be performed on the final product to determine that it meets the following standards:

(a) *Protein concentration.* The final product shall be a  $5.0 \pm 0.30$  percent solution of protein.

(b) *Protein composition.* The total protein in the final product shall consist of at least 83 percent albumin, and no more than 17 percent globulins. No more than 1 percent of the total protein shall be gamma globulin. The protein composition shall be determined by a method that has been approved for each manufacturer by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration.

(c) *pH.* The pH shall be  $7.0 \pm 0.3$  when measured in a solution of the final product diluted to a concentration of 1 percent protein with 0.15 molar sodium chloride.

(d) *Sodium concentration.* The sodium concentration of the final product shall be 130 to 160 milliequivalents per liter.

(e) *Potassium concentration.* The potassium concentration of the final product shall not exceed 2 milliequivalents per liter.

(f) *Heat stability.* A final container sample of Plasma Protein Fraction (Human) shall remain unchanged, as determined by visual inspection, after heating at  $57^{\circ}\text{C}$  for 50 hours, when compared to its control consisting of a sample, from the same lot, which has not undergone this heating.

[42 FR 27583, May 31, 1977, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990; 64 FR 26286, May 14, 1999; 65 FR 13679, Mar. 14, 2000]

#### § 640.93 General requirements.

(a) *Preservative.* The final product shall not contain a preservative.

(b) *Storage of bulk solution.* After all processing steps have been completed, the sterile bulk solution shall be stored in a manner that will ensure the continued sterility of the product, and at a temperature that shall not exceed the recommended storage temperature of

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the final product prescribed in § 610.53 of this chapter.

### § 640.94 Labeling.

In addition to the labeling requirements of §§ 610.60, 610.61, and 610.62 of this chapter, the container and package labels shall contain the following information:

(a) The osmotic equivalent in terms of plasma, and the sodium concentration in terms of a value or a range in milliequivalents per liter.

(b) The cautionary statement placed in a prominent position on the label, "Do Not Use if Turbid. Do Not Begin Administration More than 4 Hours After the Container Has Been Entered."

[42 FR 27583, May 31, 1977, as amended at 49 FR 2244, Jan. 19, 1984; 64 FR 26286, May 14, 1999]

## Subpart J—Immune Globulin (Human)

### § 640.100 Immune Globulin (Human).

(a) *Proper name and definition.* The proper name of this product shall be Immune Globulin (Human). The product is defined as a sterile solution containing antibodies derived from human plasma.

(b) *Source material.* The source material of Immune Globulin (Human) shall be plasma recovered from Whole Blood prepared as prescribed in §§ 640.1 through 640.5, or Source Plasma prepared as prescribed in §§ 640.60 through 640.76.

(c) *Additives in source material.* The source material shall contain no additives other than citrate or acid citrate dextrose anticoagulant solution, unless it is shown that the processing method yields a product free of the additive to such an extent that the safety, purity, and potency of the product will not be affected adversely.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4140, Jan. 29, 1985; 64 FR 26287, May 14, 1999]

### § 640.101 General requirements.

(a) *Heat stability test.* Approximately 2 ml. of completely processed material of each lot shall not show any visible sign of gelation after heating in a 12x75

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mm. stoppered glass tube at 57 °C for 4 hours.

(b) *pH.* The pH of final container material shall be  $6.8 \pm 0.4$  when measured in a solution diluted to 1 percent protein with 0.15 molar sodium chloride.

(c) *Turbidity.* The product shall be free of turbidity as determined by visual inspection of final containers.

(d) *Date of manufacture.* The date of manufacture is the date of initiating the last valid measles or poliomyelitis antibody test (§ 640.104(b) (2) and (3)) whichever date is earlier.

(e) *Labeling.* In addition to complying with all applicable labeling required in this subchapter, labeling shall indicate that:

(1) There is no prescribed potency for viral hepatitis antibodies.

(2) The product is not recommended for intravenous administration.

[38 FR 32089, Nov. 20, 1973; 48 FR 13026, Mar. 29, 1983, as amended at 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 51 FR 15611, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990; 63 FR 16685, Apr. 6, 1998; 64 FR 26287, May 14, 1999]

### § 640.102 Manufacture of Immune Globulin (Human).

(a) *Processing method.* The processing method shall be one that has been shown: (1) To be capable of concentrating tenfold from source material at least two different antibodies; (2) not to affect the integrity of the globulins; (3) to consistently yield a product which is safe for subcutaneous and intramuscular injection and (4) not to transmit viral hepatitis.

(b) *Microbial contamination.* Low temperatures or aseptic techniques shall be used to minimize contamination by microorganisms. Preservatives to inhibit growth of microorganisms shall not be used during processing.

(c) *Bulk storage.* The globulin fraction may be stored in bulk prior to further processing provided it is stored in clearly identified hermetically closed vessels. Globulin as either a liquid concentrate or a solid and containing alcohol or more than 5 percent moisture shall be stored at a temperature of  $-10^{\circ}\text{C}$  or lower. Globulin as a solid free from alcohol and containing less than 5 percent moisture, shall be stored at a temperature of  $0^{\circ}\text{C}$  or lower.